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GMP REQUIREMENTS FOR "BUILDINGS AND FACILITIES" FOR API – COMPARISON OF SCHEDULE M, INDIA AND ICH GUIDELINE AND APPROACH FOR COMPLIANCE TO DIFFERENT REGULATORY EXPECTATIONS

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ABSTRACT

India is one of the most attractive and promising pharmaceutical markets in the world. Majority of the Active Pharmaceutical Ingredients used in highly regulated countries are being outsourced from India and China. Globally, Indian pharma market ranks 4th in terms of generic production and 17th in terms of export value of bulk actives and dosage forms which indicates India is emerging as a universal powerhouse in the pharmaceutical business. Healthcare products marketed to a specific country should comply with Good Manufacturing Practices (GMP) regulations of that country, no matter where the products have been developed and manufactured. Unfortunately GMPs vary to some extent from country to country. On the other hand global pharmaceutical players are interested to market their products to different countries to leverage high development cost. Buildings and Facilities is a significant aspect of GMP requirements as expectations for efficient and effective manufacturing facilities is rising day by day. In light of above facts, attempt has been made to compare Indian GMP requirements w.r.t. internationally accepted ICH guideline and design approach for compliance to different regulatory expectations for "Buildings and Facilities".

Keywords: Buildings and Facilities, Good Manufacturing Practices, Active Pharmaceutical Ingredients.

INTRODUCTION

Drug industry is currently the second largest global industrial sector by market value [1]. Drug quality has become an issue of growing concern in developing countries [2]. It may lead to adverse clinical results both in terms of low efficacy and by inducing drug resistance or serious damage to patients' health [3,4,5] In several countries, there is a great

concern that the prevalence of low quality drugs is high [6]. In addition, the manufacturing of substandard medicines remains a global concern [7]. In the drug industry, quality more accurately reflects adherence to the rules as Good Manufacturing Practice (GMP) [8].

Good Manufacturing Practices (GMP)

Good Manufacturing Practices (GMP) is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. GMP are aimed primarily at diminishing the risk inherent in any pharmaceutical production which may broadly be categorized in two groups: cross contamination/mix-ups and false labelling. [9].

Worldwide, there are different official regulatory statements and guidelines, national and international, on Good Manufacturing Practices for pharmaceutical (or "drug" or "medicinal") products. They may be regulations (as in the US, Japan or Korea), directives (as in the EU), guides (as in the UK), codes (as in Australia), or WHO code (as in many Southeast Asia Countries). Out of them, following stands out as being the most influential and most frequently referenced:

- The US Current Good Manufacturing Practices for Finished Pharmaceuticals regulations (the "US cGMPs"). [10]
- The Guide to Good Manufacturing Practice for Medicinal Products of the European Union (the "EC GMP Guide"). [11]
- ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. [12]
- WHO good manufacturing practices. [13]

The other guidelines and regulation referred by the pharmaceutical manufacturers are as under

- Schedule M "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products" The Drugs And Cosmetics Act And Rules, India. [14]

- PIC/S Guide to Good Manufacturing Practice for Medicinal Products. [15]
- Centre for Drug Evaluation and Research (CDER); Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients. [16]

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body is known as API. [12]

Current status of GMP for Active Pharmaceutical Ingredients

While the production of APIs are, to a degree, the manufacture of chemicals, there are considerable additional regulatory burdens imposed on the production of APIs as they are an integral par of pharmaceuticals and there must be strict controls over the potential contaminants and cross-contaminants in the API. Therefore the design of an API facility must not contribute to any potential contamination of the API. [17] Many regulatory agencies have provided GMP guidelines for Active Pharmaceutical Ingredients (APIs). The ICH has produced the Q7 guideline describing the GMP standards for APIs. [12] This guidance is now being transposed into local and regional rules. WHO has furnished separate GMP guideline for API. [13] Drug and Cosmetics Act, India also has mentioned GMP requirements for API in revised Schedule M. [14]. Since 2005, the Indian manufacturers of API need to comply with the requirement mentioned in Schedule M.

The GMP requirement and approach of inspection fluctuates w.r.t. different regulatory agencies. For the manufacturer whose business spread internationally, has to comply the different regulatory requirement. The overseas customers are not interested in manufacturer unless the API manufacturer sticks to the latest certification of the highest quality norms. They also have to satisfy regulatory agencies and their customers for GMP systems and for that they have to keep track and maintain multiple records to fulfill different regulatory and customers expectations.

The 10 Golden Rules of GMP: [18]

The Table 1 describes the 10 Golden Rules of GMP. Rule no. 3 and 5 describes the importance of Documentation and Records.

TABLE 1: THE 10 GOLDEN RULES OF GMP

Number	The Golden Rule of GMP
1	Get the facility design right from the start
2	Validate processes
3	Write good procedures and follow them
4	Identify who does what
5	Keep good records
6	Train and develop staff
7	Practice good hygiene
8	Maintain facilities and equipment
9	Build quality into the whole product lifecycle
10	Perform regular audits

Rule 1 and Rule 9 emphasize the compliance of GMP requirement of Buildings and Facilities

Facility layout

Layout the production area to suit the sequence of operations. The aim is to reduce the chances of cross contamination and to avoid mix-ups and errors. For example, don't have final product passing through or near areas that contain intermediate products or raw materials. A logical and well-planned layout will improve productivity. Sometimes you need to step back and reconsider the whole production area rather than applying quick fix solutions. Aim to:

- Remove unnecessary traffic in the production area which could result in a hazardous environment
- Segregate materials, products, and their components to minimise confusion and potential for mix-ups and errors.

Environment

It's important to control the air, water, lighting, ventilation, temperature, and humidity within a plant so that it does not impact product quality. You should design facilities to reduce the risk of contamination from the environment. Make sure that:

- § Lighting, temperature, humidity and ventilation are appropriate
- § Interior surfaces (walls, floors and ceilings) are smooth, free from cracks and do not shed particulate matter
- § Interior surfaces are easy to clean
- § Pipe work, light fittings, and ventilation points are easy to clean
- § Drains are sized adequately and have trapped gullies.

Equipment

Design, locate, and maintain equipment to suit its intended use. Make sure that equipment is:

- § Easy to repair and maintain
- § Designed and installed in an area where it can be easily cleaned
- § Suitable for its intended use
- § Not reactive, additive or absorptive
- § Calibrated at defined intervals (if necessary)
- § Clearly labelled.

Maintain facilities and equipment

It's important to have a maintenance schedule for facilities and equipment. Regular equipment maintenance prevents equipment breakdowns, which can be costly. It also reduces the risk of product contamination and maintains the 'validated state' of the facility or equipment. Sometimes an unexpected event may affect the facility or equipment and under such circumstances, you need to carry out repairs immediately. You should have written procedures for all scheduled and emergency maintenance. These should detail who does the work, the tasks involved, and define any lubricants, coolants,

cleaning agents etc. required. It's also a GMP requirement to have a maintenance schedule in place with the frequency determined by the criticality of the equipment.

COMPARISON OF SCHEDULE M, INDIA WITH ICH Q7 FOR BUILDING AND FACILITIES REQUIREMENT

International Conference on Harmonization (ICH) [19]

The ICH was established in 1990. Its main aim is to improve the efficiency of the drug development process and the registration of new drug products in its member countries through harmonization of national guidelines. This is a joint initiative involving both regulators and industry as equal partners. The founders and current members of ICH, which represent the regulatory bodies and the research-based industry in the member countries, are the EU, European Federation of Pharmaceutical Industries and Associations (EFPIA), Ministry of Health, Labor and Welfare (MHLW), Japan Pharmaceutical Manufacturers Association (JPMA), Food and Drug Administration US (FDA) and Pharmaceutical Research and Manufacturers of America (PhRMA). Among other guidelines, ICH has also published a guide on GMP for APIs (Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients). It is intended to provide guidance regarding GMP for the manufacture of APIs and to help ensure that APIs meet the quality and purity requirements that they are presented to possess. It consists of 19 chapters.

Schedule M, India [19]

The production of drug products (drugs) in India is controlled under the Drugs and Cosmetics Rules (1945, last amended in 2005), which states that the holder of the license to manufacture drugs has to comply with the requirements of GMP as laid down in Schedule M. Schedule M is a part of the Drugs and Cosmetics Rules and embodies the Indian GMP regulations, which are based on the 1982 version of WHO GMP guidelines. Indian GMP regulations consists of eight parts: I, IA, IB, IC, ID, IE, IF and II. Part I covers the general requirements of GMP. It is divided into 29 chapters. Parts IA to IE

cover specific requirements for manufacture of different dosage forms regarding premises, equipment, and methods. Part 1F covers specific requirements for the manufacture of APIs regarding buildings and facilities, utilities, equipment, controls, and containers. Part II of the Indian GMP regulations consist of detailed recommendations for the process equipment to be used in the manufacture of different dosage forms and requirements for the partition of the production area.

Comparison of ICH and Schedule M, India for Building and Facilities requirements is highlighted in Table 2. The different requirement of Schedule M, India has been mentioned along with the respective requirement of ICH. This may be useful to understand the GMP requirements of both.

TABLE 2: COMPARISON OF ICH AND SCHEDULE M, INDIA W.R.T GMP REQUIREMENTS OF BUILDINGS AND FACILITIES

ICH Q7	SCHEDULE M, INDIA
DESIGN AND CONSTRUCTION	
4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate	**Part-1-1.1** The factory building(s) for manufacture of drugs shall be so situated and shall have such measures as to avoid risk of contamination from external environment including open sewage, drain, public lavatory or any factory which produce disagreeable or obnoxious odour or fumes, excessive soot, dust, smoke, chemical or biological emissions
	Part-1-1.2(i) compatible with other drug manufacturing operations that may be carried out in the same or adjacent area / section
	Part-1-1.2 The building(s) used for the factory shall be designed, constructed, adapted and maintained to suit the manufacturing operations so as to permit production of drugs under hygienic conditions. They shall conform to the conditions laid down in the Factories Act,

TABLE 2: COMPARISON OF ICH AND SCHEDULE M, INDIA W.R.T GMP REQUIREMENTS OF BUILDINGS AND FACILITIES	
ICH Q7	**SCHEDULE M, INDIA**
	1948 (63 of 1948)
4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination	**Part-1-1.2(ii) / Part-1-3.3** adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to: (a) avoid the risk of mix-up between different categories of drugs or with raw materials, intermediates and in-process material; (b) avoid the possibilities of contamination and cross- contamination by providing suitable mechanism;
	Part-1-1.2(vi) the walls and floors of the areas where manufacture of drugs is carried out shall be free from cracks and open joints to avoid accumulation of dust. These shall be smooth, washable, coved and shall permit easy and effective cleaning and disinfection. The interior surfaces shall not shed particles. A periodical record of cleaning and painting of the premises shall be maintained
4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment may be located outdoors	
4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination	**Part-1-3.1** The production area shall be designed to allow the production preferably in uni-flow and with logical sequence of operations.
4.14 There should be defined areas or other control systems for the following activities: • Receipt, identification, sampling, and quarantine of incoming materials,	**Part-1-10.7** There shall be adequate separate areas for materials “under test”, “approved” and “rejected” with arrangements and equipment to allow dry, clean and orderly placement of stored materials and products,

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ICH Q7	**SCHEDULE M, INDIA**
• pending release or rejection; • Quarantine before release or rejection of intermediates and APIs; • Sampling of intermediates and APIs; • Holding rejected materials before further disposition (e.g., return, • reprocessing or destruction); • Storage of released materials; • Production operations; • Packaging and labelling operations; and Control and • laboratory operations.	wherever necessary, under controlled temperature and humidity.
	Part-1-2.5 There shall be a separate sampling areas in the warehousing area for active raw materials and excipients. If sampling is performed in any other area, it shall be conducted in such a way as to prevent contamination, cross-contamination and mix-up.
	Part-1-2.6 Segregation shall be provided for the storage of rejected, recalled or returned materials or products shall be suitably marked and secured. Access to these areas and materials shall be restricted.
	Part-1-2.3 Receiving and dispatch bays should protect materials and products from the weather condition
4.15 Adequate and clean washing facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as necessary, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided when appropriate.	**Part-1-4.2** Facilities for changing, storing clothes and for washing and toilet purposes shall be easily accessible and adequate for the number of users. Toilets, separate for males and females, shall not be directly connected with production or storage areas. There shall be written instructions for cleaning and disinfection of such areas.
	Part-1-4.1 Rest and refreshment rooms shall be separate from other areas. These areas shall not lead directly to the manufacturing and storage areas.
	Part-1-4.3 Maintenance workshops shall be separate and away from production areas. Whenever spares, changed parts and tools are stored in the production area, these shall be kept in dedicated rooms or lockers. Tools and

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ICH Q7	**SCHEDULE M, INDIA**
	spare parts for use in sterile areas shall be disinfected before these are carried inside the production areas.
	Part-1-4.4 Areas housing animals shall be isolated from other areas. The other requirements regarding animal houses shall be those as prescribed in rule 150-C(3) of the Drugs and Cosmetics Rules, 1945 which shall be adopted for production purposes.
4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, may be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.	**Part-1-5.1.** Quality Control Laboratories shall be independent of the production areas. Separate areas shall be provided each for physico-chemical, biological, microbiological or radio-isotope analysis. Separate instrument room with adequate area shall be provided for sensitive and sophisticated instruments employed for analysis.
	Part-1-16.2 The area of the quality control laboratory may be divided into Chemical, Instrumentation, Microbiological and Biological testing.
	Part-1-5.2 Quality Control Laboratories shall be designed appropriately for the operations to be carried out in them. Adequate space shall be provided to avoid mix-ups and cross-contamination. Sufficient and suitable storage space shall be provided for test samples, retained samples, reference standards, reagents and records.
	Part-1-5.4. Quality Control Laboratory shall be divided into separate sections i.e. for chemical, microbiological and wherever required, biological testing. These shall have adequate area for basic installation and for ancillary purposes. The microbiology section shall have arrangements such as airlocks and

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ICH Q7	**SCHEDULE M, INDIA**
	laminar air flow work station, wherever considered necessary.
	Part-1- 5.3 The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall be provided for biological, microbiological and radioisotopes testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.
UTILITIES	
4.20 All utilities that could impact on product quality (e.g. steam, gases, and compressed air) should be qualified and appropriately monitored to ensure that specifications are met and action is taken when limits are exceeded.	
4.21 Adequate ventilation and exhaust systems should be provided, where necessary. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment	**Part-1-1.2(iv)** The premises used for manufacturing, processing, warehousing, packaging, labeling & testing shall be air-conditioned, where prescribed for the operations and dosage forms under production. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units (wherever applicable) to maintain conditions including temperature and, wherever necessary, humidity, as defined for the relevant product.

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ICH Q7	**SCHEDULE M, INDIA**
	These conditions shall be appropriate to the category of drugs and nature of the operation. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications;
	Part-1-F-1.2 The final stage of preparation of a drug, like isolation/filtration/drying/ milling / sieving and packing operations shall be provided with air filtration systems including pre-filters and finally with a 5 micron filter. Air handling systems with adequate number of air changes per hour or any other suitable system to control the air borne contamination shall be provided. Humidity / Temperature shall also be controlled for all the operations wherever required
4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination	**Part-1-F-1.3** Air filtration systems including pre-filters and particulate matter retention air filters shall be used, where appropriate, for air supplies to production areas. If air is re-circulated to production areas, measures shall be taken to control re-circulation of floating dust particles from production. In areas where air contamination occurs during production, there shall be adequate exhaust system to control contaminants

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ICH Q7	**SCHEDULE M, INDIA**
4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API	**Part-1-3.4** Pipe-work, electrical fittings, ventilation openings and similar service lines shall be designed, fixed and constructed to avoid accumulation of dust. Service lines shall preferably be identified by colours and the nature of the supply and direction of the flow shall be marked / indicated.
	Part-1-F-1.4 Ancillary area shall be provided for Boiler-house. Utility areas like heat exchangers, chilling workshop, store and supply of gases shall also be provided
4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate	**Part-1-1.2 (v)** provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back- flow and/or prevent insects and rodents entering the premises. Open channels shall be avoided in manufacturing areas and, where provided, these shall be shallow to facilitate cleaning and disinfection
WATER	
4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use	**Part-1--1.3** There shall be validated system for treatment of water drawn from own or any other source to render it potable in accordance with standards specified by the Bureau of Indian Standards or Local Municipality, as the case may be, so as to produce Purified Water conforming to Pharmacopoeial specification. Purified Water so produced shall only be used for all the operations except washing and cleaning operations where potable water may be used. Water shall be stored in tanks, which
4.31 Unless otherwise justified, process water should, at a minimum, meet national standards for potable water that have been documented as at least equivalent to World Health Organization (WHO) guidelines. In the absence of national standards, WHO guidelines should be used.	

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ICH Q7	**SCHEDULE M, INDIA**
4.32 If potable water standards are insufficient to assure API quality and tighter chemical and microbiological water quality specifications are necessary, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established	do not adversely affect quality of water and ensure freedom from microbiological growth. The tank shall be cleaned periodically and records maintained by the licensee in this behalf
4.33 Where water used in the process is treated by the manufacturer to achieve defined quality, the treatment process should be validated and monitored with appropriate action limits	
4.34 Where the manufacturer of a non-sterile API either intends or claims that it is suitable to be used in further processing to produce a sterile drug (medicinal) product, then water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins	
CONTAINTMENT	
4.40 Dedicated production areas, which may include such facilities as air handling equipment and/or process equipment, should be employed in the production of each type of highly sensitizing material (e.g., penicillins or cephalosporins)	**Part-1-F-1.1 / Part-1-3.2** Apart from the building requirements contained in Part I, General ante, the active pharmaceutical ingredients facilities for manufacture of hazardous reactions, Beta-Lactum antibiotics. Steroids and Steroidal Hormones / Cytotoxic substances shall be provided in confined areas to prevent contamination of the other drugs manufactured
	Part-1-5.17 Normally, the production of non-medicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.
4.41 Dedicated production areas should also	**Part-1-F-1.5** For specified preparation like

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ICH Q7	**SCHEDULE M, INDIA**
be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.	manufacture of sterile products and for certain antibiotics, sex hormones, cytotoxic and oncology products, separate enclosed areas shall be designed. The requirements for the sterile active pharmaceutical ingredient shall be in line with the facilities required for formulation to be filled aseptically
	Part-1-2.10 Sampling and dispensing of sterile materials shall be conducted under aseptic conditions conforming to Grade A, which can also be performed in a dedicated area within the manufacturing facility.
4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another	
4.43 Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.	**Part-1-2.9** separate dispensing areas for ß (Beta) lactum, Sex Hormones and Cytotoxic substances or any such special categories of product shall be provided with proper supply of filtered air and suitable measures for dust control to avoid contamination. Such areas shall be under differential pressure
	Part-1-F-2 Sterile active pharmaceutical ingredient filled aseptically shall be treated as formulation from the stage wherever the process demands like crystallization, Lyophilisation, filtration etc. All conditions applicable to formulations that are required to be filled aseptically shall apply *mutatis mutandis* for the manufacture of sterile active

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ICH Q7	**SCHEDULE M, INDIA**
	pharmaceutical ingredients involving stages like filtration, crystallization and lyophilisation.
	Part-1-F-3 Equipment like chilling plant, boiler, heat exchangers, vacuum and gas storage vessels shall be serviced, cleaned, sanitized and maintained at appropriate intervals to prevent mal-functions or contamination that may interfere with safety, identity, strength, quality or purity of the drug product.
LIGHTING	
4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.	**Part-1- 1.2(iv)** The production and dispensing areas shall be well lighted
	Part-I-9.5 Production areas shall be well lit, particularly where visual on-line controls are carried out.
SEWAGE AND REFUSE	
4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.	**Part-1- (1.4)** Disposal of waste. - • The disposal of sewage and effluents (solid, liquid and gas) from the manufactory shall be in conformity with the requirements of Environment Pollution Control Board. • All bio-medical waste shall be destroyed as per the provisions of the Bio-Medical Waste (Management and Handling) Rules, 1996. • Additional precautions shall be taken for the storage and disposal of rejected drugs. Records shall be maintained for all disposal of waste. • Provisions shall be made for the proper and safe storage of waste materials awaiting disposal. Hazardous, toxic substances and flammable materials shall be stored in suitably designed and

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ICH Q7	**SCHEDULE M, INDIA**
	segregated, enclosed areas in conformity with Central and State Legislations.
SANITATION AND MAINTENANCE	
4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition	
4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.	
4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labelling materials, intermediates, and APIs.	**Part-1-1.2(iii)** The premises used for manufacturing, processing, warehousing, packaging, labelling and testing purposes shall be designed / constructed / maintained to prevent entry of insects, pests, birds, vermins and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection
	Part-1-2.12 Rodent treatments (Pest control) should be done regularly and at least once in a year and record maintained
	Part-II : *Covers the requirements of plant and equipment for different types of dosage forms*

Highlights

Design and Construction:

-ICH has no specific mention about keeping records for periodic painting of premises

-Schedule M demands the receiving and dispatch bays to protect the incoming material

-Schedule M has specific mention about rest and refreshment room and maintenance workshop should be separated from production areas.

-Schedule M has mention regarding separate air handling units and other requirements shall be provided for biological, microbiological and radioisotopes testing areas.

Utilities:

-Schedule M has mention that comfort cooling is required for personnel working in the different area.

-Schedule M specifically mentioned that Final purification steps should be carried out in the area which is equipped with 5micron filtered clean air.

-pipeworks should have identity of content and flow direction as per Schedule M

Containment:

-As per ICH, dedicated area is required for production of highly sensitizing materials.

-Schedule M has mention that_Equipment like chilling plant, boiler, heat exchangers, vacuum and gas storage vessels shall be serviced, cleaned, sanitized and maintained at appropriate intervals to prevent mal-functions or contamination that may interfere with safety, identity, strength, quality or purity of the drug product

Sanitation and Maintenance:

-Schedule M has mention of frequency for Rodent treatment and pest control

COMPREHENSIVE REQUIREMENT:

Note: *The comprehensive requirement prepared by referring above mentioned guidance documents / regulatory requirement.* [10-16]

1 Design and construction

- Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as

appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate

- The premises used for manufacturing, processing, warehousing, packaging, labelling and testing purposes shall be designed / constructed / maintained to prevent entry of insects, pests, birds, vermins and rodents. Interior surface (walls, floors and ceilings) shall be smooth and free from cracks, and permit easy cleaning, painting and disinfection. The interior surfaces shall not shed particles. A periodical record of cleaning and painting of the premises shall be maintained.
- Steps should be taken in order to prevent the entry of unauthorized people. Production, storage and quality control areas should not be used as a right of way by personnel who do not work in them.
- Buildings and facilities should adequately provided with working space to allow orderly and logical placement of equipment, materials and movement of personnel so as to: (a) avoid the risk of mix-up between different categories of drugs or with raw materials, intermediates and in-process material; (b) avoid the possibilities of contamination and cross- contamination by providing suitable mechanism;
- Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.
- Equipment for the adequate control and monitoring of air pressure, microorganisms, dust, humidity, and temperature should be provided when appropriate (e.g., when APIs are exposed to the environment or handled in the final dry state)

- Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment may be located outdoors
- The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination
- There shall be adequate separate areas for materials “under test”, “approved” and “rejected” with arrangements and equipment to allow dry, clean and orderly placement of stored materials and products, wherever necessary, under controlled temperature and humidity.
- There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination
- Receiving and dispatch bays should protect materials and products from the weather condition.
- Adequate and clean washing facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as necessary, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided when appropriate.
- Rest and refreshment rooms should be separate from other areas.
- Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
- If API requires animal testing, animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.
- Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, may be located in

production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

- The area of the quality control laboratory may be divided into Chemical, Instrumentation, Microbiological and Biological testing.
- Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records
- Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, etc
- The design of the laboratory shall take into account the suitability of construction materials and ventilation. Separate air handling units and other requirements shall be provided for biological, microbiological and radioisotopes testing areas. The laboratory shall be provided with regular supply of water of appropriate quality for cleaning and testing purposes.

2 Utilities

- Steam that comes into contact with APIs and intermediates should be tested and monitored to ensure that it is of suitable quality and devoid of contaminants, such as boiler additives, that could adversely affect API quality. All other utilities (e.g., gases, compressed air) that come into contact with APIs and intermediates should comply with appropriate specifications and not alter API quality beyond its established specifications.
- The premises used for manufacturing, processing, warehousing, packaging, labeling & testing shall be air-conditioned, where prescribed for the operations and product type. The production and dispensing areas shall be well lighted, effectively ventilated, with air control facilities and may have proper Air Handling Units (wherever applicable) to maintain conditions including temperature and, wherever necessary, humidity, as

defined for the relevant product. These conditions shall be appropriate to the category of drugs and nature of the operation. These shall also be suitable to the comforts of the personnel working with protective clothing, products handled, operations undertaken within them in relation to the external environment. These areas shall be regularly monitored for compliance with required specifications;

- There should be adequate exhaust system to protect the environment.
- The final stage of preparation of a drug, like isolation/filtration/drying/ milling / sieving and packing operations shall be provided with air filtration systems including pre-filters and finally with a HEPA filter. Where products are not being exposed to the environment, the 5micron filter can be used if justified. Air handling systems with adequate number of air changes per hour or any other suitable system to control the air borne contamination shall be provided. Humidity / Temperature shall also be controlled for all the operations wherever required
- Air filtration systems including pre-filters and particulate matter retention air filters shall be used, where appropriate, for air supplies to production areas. If air is re-circulated to production areas, measures shall be taken to control re-circulation of floating dust particles from production. In areas where air contamination occurs during production, there shall be adequate exhaust system to control contaminants
- Pipework, light fittings, ventilation points and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.
- Fixed pipework should be clearly labelled to indicate the contents and, where applicable, the direction of flow.
- Ancillary area shall be provided for Boiler-house. Utility areas like heat exchangers, chilling workshop, store and supply of gases shall also be provided
- Equipment like chilling plant, boiler, heat exchangers, vacuum and gas storage vessels

shall be serviced, cleaned, sanitized and maintained at appropriate intervals to prevent mal-functions or contamination that may interfere with safety, identity, strength, quality or purity of the drug product.

- Required area shall be provided with drainage system, as specified for the various categories of products, which shall be of adequate size and so designed as to prevent back- flow and/or prevent insects and rodents entering the premises. Open channels shall be avoided in manufacturing areas and, where provided, these shall be shallow to facilitate cleaning and disinfection

3 Water

- Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use
- Distilled, deionized and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
- Potable water should be supplied under continuous positive pressure in a plumbing system free from defects that could lead to the contamination of APIs or intermediates. Potable water should meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations
- If potable water standards are insufficient to assure API quality and tighter chemical and microbiological water quality specifications are necessary, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established
- Where water used in the process is treated by the manufacturer to achieve defined quality, the treatment process should be validated and monitored with appropriate action limits
- Where the manufacturer of a non-sterile API either intends or claims that it is suitable to be used in further processing to produce a sterile drug (medicinal) product, then water

used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins

4 Containment

- Dedicated production areas, which may include such facilities as air handling equipment and/or process equipment, should be employed in the production of each type of highly sensitizing material (e.g., penicillins or cephalosporins)
- Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anti-cancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.
- API manufacturing processes that require viral inactivation or reduction should be appropriately segregated (e.g., pre- and post viral inactivation or reduction activities).
- Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another
- Any production activities (including weighing, milling, or packaging) of highly toxic non-pharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.
- Sterile API filled aseptically shall be treated as formulation from the stage wherever the process demands like crystallization, Lyophilisation, filtration etc. All conditions applicable to formulations that are required to be filled aseptically shall apply for the manufacture of sterile API involving stages like filtration, crystallization and lyophilisation.
- Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled

release of dust, gases, vapours, sprays or organisms from materials and products in process, from residues on equipment, and from operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Amongst the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

- Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

5 Lighting Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

6 Sewage and refuse

- Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.
- All bio-medical waste shall be destroyed as per the provisions of the National rules for Bio-Medical Waste.
- Additional precautions shall be taken for the storage and disposal of rejected drugs. Records shall be maintained for all disposal of waste.
- Provisions shall be made for the proper and safe storage of waste materials awaiting disposal. Hazardous, toxic substances and flammable materials shall be stored in suitably designed and segregated, enclosed areas in conformity with Central and State Legislations

7 Sanitation and maintenance

- Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors and ceilings) should be

smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection

- Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities. Such written procedures should be followed. Sanitation procedures should apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations
- Written procedures should also be established for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging materials, labeling materials, intermediates, and APIs. Rodenticides, insecticides, and fungicides should be registered and applied according to locally applicable regulations.

Approach for Compliance :

- ø It is important to realize hat API manufacturing plants are designed and constructed in various different ways depending on the chemistry, the nature of the API, the location of the plant and GMP philosophy of the individual company etc.
- ø An increase of product protection is expected from early steps to the final API, especially for areas where open handling of the API without further purification is performed (e.g. Drying, milling, weighing and packaging etc.)
- ø <u>Construction materials:</u>

  Walls: The position of walls should provide an orderly movement of materials and personnel. Noise levels should also taken into consideration the interrelationship of different operations should minimize the potential for cross-contamination and mix-ups. Walls in manufacturing area should be of plaster finish on high-quality concrete blocks or gypsum board. The finish should be smooth, usually with enamel or epoxy paint

  Floors: Floor covering should be selected for durability as well as cleanability. Resistance to the chemicals also taken into account.

Ceilings: Suspended ceilings may be provided in office area. Manufacturing area require smooth finish, often seamless plaster or gypsum board.

Utilities: In the building design, provisions must be made for drains, water, steam and electricity and other utilities for ease of maintenance. Access should, ideally, be possible without disruption of activity within the actual rooms provided with the services. Compressed air coming in contact with product should be oil free.

- Air handling system: Where recirculation of air is allowed, adequate precautions to ensure that particulates from a processing area are removed. Temperature and humidity conditions should provide personnel comfort. Where differential pressures are required between adjacent areas suitable monitoring device e.g. magnahelic gauge should be in place. Air intakes should be positioned away from potential sources of contamination
- Water & Drain: Bore-well water should be tested periodically for pesticide content. There shall be appropriate specification for potable water and process water. The water should be supplied under continuous positive pressure in a defect free plumbing system. Adequate size drain shall be provided with an air break to prevent back-siphonage.
- Pest Control: Contract for pest control activity should be available and followed.
- Lay out: Following lay out should be in place.

  Manufacturing area lay out, Air Flow pattern in HVAC/AHU lay out of manufacturing area, Utility lay out (water, steam, drain), and Electrical lay out.

  Any change in buildings and facility should be routed through change control procedure and impact analysis for associated validation activities.
- Sanitation and Maintenance: cleaning of accidental spills and routine cleaning programme should be defined with rotation of validated disinfectants. External contractors are often used for sanitation and facility cleaning activities. They should be trained in GMP and their responsibilities.
- Following SOP should be available and followed.
  - Cleaning and Sanitation of manufacturing area

- Preventive maintenance of Buildings and Facility
- Operation and preventive maintenance of water system
- Sampling and testing of Water
- Environment monitoring (Differential pressure, Temperature, Humidity and Microbial Count)
- Performance check of Utilities
- Performance check of Water and HVAC system
- Control measures adopted for prevention of cross contamination
- Pest control

ø Following qualification records should be available

- Facility Qualification (Design description and its rationale)
- AHU/HVAC Qualification
- Area Qualification
- Water System Qualification
- Utility Qualification

Following checklist may be helpful to manufacturer for assessment of compliance w.r.t. Buildings and Facilities requirement

S.No.	Checkpoints
1.	Is premises situated in appropriate location to prevent cross contamination?
2.	Are there adequate laboratory facilities to perform required testing?
3.	Is toxic/sensitizing material being produced in the premises? Is there suitable procedure to prevent cross contamination?
4.	Is facility permits easy cleaning?
5.	SOP for cleaning available?
6.	Is segregated area available for following? • Production • QC • Quarantine, Approved or Reject • Packaging and Labeling
7.	Is washing area & Toilet separated from production area?
8.	Is there proper segregation available for production & In-process control area?

S.No.	Checkpoints
9.	Is there procedure for periodic checks of utilities for its required quality? (Compressed Air, Steam, Nitrogen gas used in production are with appropriate quality?)
10.	Drawings for utilities available?
11.	Are production areas that present potential for contamination properly controlled and equipped with exhaust or other appropriate systems, including prevention of microbial contamination?
12.	If air is recirculated to areas where product is exposed, is it filtered and controlled to eliminate cross-contamination? Is there procedure and record available for periodic checks and replacement of filters?
13.	Is purification of API is carried out in controlled environment?
14.	AHU/HVAC systems are qualified?
15.	Is appropriate demarcation available on pipework to identify the content and flow direction?
16.	Are ducts and pipings installed appropriately to minimize contamination?
17.	Is water being utilized for process or cleaning of equipments?
18.	Is type of water used appropriate to its intended use?
19.	Is there a procedure available for periodic checking of quality of bore-well water according to its approved specification? Is content of pesticide part of specification?
20.	Is procedure for periodic testing process water is available with appropriate specification?
21.	Is facility for water testing is appropriate? If testing is contracted out, Is contract available for testing of water?
22.	Is process water being monitored for chemical and microbial quality?
23.	Is procedure available for periodic sanitation of storage tank and distribution line of water? Is effectiveness of sanitation process monitored and documented?
24.	Is alert and action limit defined for chemical and microbial parameter of process water?
25.	If water is outsourced, appropriate certificate is available to assure the quality of water? Any in-house checks available to reassure the water quality?
26.	Is there procedure available for frequent sampling and testing of water?
27.	Are any toxic or sensitizing materials being produced in the facility? If yes, Is adequate precautions are taken to prevent cross-contamination?
28.	Is there adequate lighting in the facility?
29.	Is the lighting protected from shattering in areas where the product may be exposed?
30.	Is there procedure available for disposal of waste?

S.No.	Checkpoints
31.	Are drains with adequate size available in the production area wherever applicable? Where the product is open to the environment, drains equipped with an air break or other mechanism to prevent back flow?
32.	Is the plumbing system free of defects that could cause contamination of the API?
33.	Is there procedure for decontamination of drain available in the area where product is being exposed?
34.	Is Washing & Toilet facilities adequate? Following are available? • Hot & cold water • Soap or detergent • Air dryers • Single service towels • Clean toilet facility • Showering/changing cloths
35.	Are container/pipes for waste material identified clearly?
36.	Is procedure for cleaning & sanitation available?
37.	Is there system for periodic rotation of cleaning agent?
38.	Is schedule for cleaning available?
39.	Are windows, doors, or other openings to the outside adequately protected from entry by pests?
40.	Is procedure for periodic pest control is available? Is use of rodenticides, herbicides and pesticides appropriately evaluated w.r.t. safety and contamination aspects?
41.	If an outside party performs pest control, is that party's performance and compliance monitored? Does the party use a site map and issue a report? Is the report reviewed by the manufacturer?
42.	Are pest control records kept for different area defined in the SOP?

CONCLUSION:

Pharmaceutical manufacture and regulation is clearly an international business. With the increasing emphasis on harmonization efforts and standard setting along with mutual recognition agreements, knowledge of foreign regulations is a necessity for both understanding the future direction of these efforts as well as for international supply of drug products. It is revealed that requirement of Buildings and Facilities in Schedule M, India can be comparable with the requirement of ICH and current requirement can very

well assure the quality of final product. However, implementation of stringent requirement may enhance the satisfaction of international customers and regulators. It is anticipated that the mentioned approach will be a useful tool for identifying gaps w.r.t. different regulatory requirement followed by comparative analysis and useful reference work quality assurance professionals for assessment of compliance during self inspection.

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